2-sided

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Dr. M. Delbrück,
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Dear Max:

Fritz Kauffmann (State Serum Institute, Copenhagen), having lost your address asks me to write to you concerning cultures of E. coli B, phage-resistant mutants. He received in moribund condition the ones you left with Dr. Toft, and asks that you send him fresh transfers on agar slopes. I have just myself sent him cultures of K-12 mutants for serological typing.

Aside from this errand, I have been looking for an occasion to write to you, because of your remarks at the 1946 CSH meeting concerning the "1:1" theory. I had reached essentially the same skeptical conclusions that you had, and on coming to Madison have set out to test the hypothesis, using E. coli and lactose-splitting for the enzymatic system. Using EMB indicator medium, and UV-induced mutations, several dozen lactose-negative mutants have been collected, and then compared phenotypically and genetically. Judging from the occurrence of Lac+ recombinants, and with adequate precautions concerning spontaneous reversion, there seem to be at least seven loci represented among these mutants. Most of them are specific for lactose; one is not, but is also maltose- and glucose-. This mutant (W-108) is of special interest, because in addition to reverse mutations, suppressor mutations occur which are glucose+, lac-, mal-. In addition there is another suppressor mutation which is Glu-, Lac+, Mal-. The two suppressors can be gotten in the same stock: Glu+, Lac+, Mal-. By reverse-mutation this can then be restored to the original phenotype: glu+, Lac+, Mal+. All these strains can utilize galactose. Attempts to separate the Glu-Lac-Mal- components of the W-108 stock by recombination have been unsuccessful, but the strongest evidence that a "single gene change" is involved is the frequent occurrence of reverse mutations which simultaneously restore all three functions. In addition, then, to the apparent occurrence of seven distinct mutations related to one enzymatic function, a single mutation may be pleiotropic, while diverse effects of this mutation may be suppressed by mutation of other loci.

However, in addition to the objections that might be raised as to the number of enzymes actually involved in lactose splitting (seven is absurd!), there is a more deep-seated difficulty which arises from the adaptive nature of microbial enzymes. We know that enzyme formation, or rather activity, is not an inexorable consequence of the presence of the appropriate genetype, but depends on a variety of other conditions, including pH, temperature, presence of substrate and

substrate analogues (e.g. Neurospora 16117), that we know about and, presumably therefore, on some unknown intracellular conditions. Therewe cannot conolude from the behavior of a mutant genotype that the function of the normal allelomorph has been in any specific way the production of a given enzyme. The only methods we have for check on the 1:1 theory deal with the analysis of pleiotropic mutations on the one hand, and complementary mutations on the other. The hypothesis is therfore experimentally unverifiable, and in terms of the gene defined in any genetic way, meaningless. In terms of the material gene, e.g. nucleoprotein active in a transforming system, or responding to Emerson's antibodies, there may be some hope, but I have come to be very suspicious of more strictly genetic support of the so-called template hypothesis. After all, is it not possible that enzyme specificity, like antibody specificity, is closely controlled by the substrate, and that the function of the genes is to provide the undifferentiated pro-enzymes, corresponding to normal gamma globulin?

Aside from suggesting a lazy "it is too complex" note in answering genetic problems, the only important effect of this philosophy is in the application of mutants to biochemical problems. It may be, then, questionable, whether a single gene mutation blocks only one step in a biosynthesis, and correspondingly, whether the participation of several loci in a block between two compounds necessitated that there be more than one enzyme doing that job.

Before too long, I hope to write up this material, but before doing so I should like to have some notions of the current Caltech viewpoints. I would then be glad to hear your reactions.

Best regards,

Sincerely,

Joshua Lederberg